General

Guideline Title

Guideline for reversal of antithrombotics in intracranial hemorrhage: a statement for healthcare professionals from the Neurocritical Care Society and Society of Critical Care Medicine.

Bibliographic Source(s)

Frontera JA, Lewin JJ III, Rabinstein AA, Aisiku IP, Alexandrov AW, Cook AM, del Zoppo GJ, Kumar MA, Peerschke EI, Stiefel MF, Teitelbaum JS, Wartenberg KE, Zerfoss CL. Guideline for reversal of antithrombotics in intracranial hemorrhage: a statement for healthcare professionals from the Neurocritical Care Society and Society of Critical Care Medicine. Neurocrit Care. 2016 Feb;24(1):6-46. [434 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Definitions of the strength of recommendations (*strong*, *conditional*, *good practice*) and quality of the evidence (*high*, *moderate*, *low*, *very low*) are provided at the end of the "Major Recommendations" field.

Recommendations for Vitamin K Antagonists (VKA) Reversal

1. The authors recommend discontinuing VKAs when intracranial hemorrhage is present or suspected. (*Good Practice statement*)
2. The authors recommend urgent reversal of VKAs in patients with intracranial hemorrhage (*Strong recommendation, moderate-quality evidence*) with the following considerations:
    a. The authors suggest against VKA reversal in patients where there is a high suspicion of intracranial hemorrhage due to cerebral venous thrombosis. (*Conditional recommendation, very low-quality evidence*)
    b. The authors recommend assessing risks and benefits when considering VKA reversal in intracranial hemorrhage patients with concurrent symptomatic or life-threatening thrombosis, ischemia, heparin-induced thrombocytopenia, or disseminated intravascular coagulopathy (DIC). (*Good Practice statement*)
3. The authors recommend administration of vitamin K to ensure durable reversal of international normalizing ratio (INR) following VKA-associated intracranial hemorrhage. Vitamin K should be dosed as soon as possible or concomitantly with other reversal agents. (*Strong recommendation, moderate-quality evidence*)

    a. The authors suggest one dose of vitamin K 10 mg intravenous [IV]). Subsequent treatment should be guided by follow-up INR. (*Good Practice statement*)
    b. If repeat INR is still elevated ≥1.4 within the first 24 to 48 h after reversal agent administration, the authors suggest redosing with vitamin K 10 mg IV. (*Good Practice statement*)
4. The authors recommend administering 3-factor or 4-factor prothrombin complex concentrates (PCC) rather than fresh frozen plasma (FFP) to patients with VKA-associated intracranial hemorrhage and INR ≥1.4. (*Strong recommendation, moderate-quality evidence*)
    a. The authors suggest the use of 4-factor PCC over 3-factor PCC. (*Conditional recommendation, low-quality evidence*)
    b. The authors suggest initial reversal with PCC alone (either 3- or 4-factor) rather than combined with FFP or recombinant factor VIIa (rFVIIa). (*Conditional recommendation, low-quality evidence*)
    c. The authors recommend that PCC dosing should be weight-based and vary according to admission INR and type of PCC used. (*Strong recommendation, moderate-quality evidence*)
    d. The authors recommend repeating INR testing soon after PCC administration (15–60 min), and serially every 6 to 8 h for the next 24 to 48 h. Subsequent treatment should be guided by follow-up INR, with consideration given to the fact that repeat PCC dosing may lead to increased thrombotic complications and risk of DIC. (*Good Practice statement*)
    e. If the repeat INR is still elevated ≥1.4 within the first 24–48 h after initial PCC dosing, the authors suggest further correction with FFP. (*Conditional recommendation, low-quality evidence*)
5. The authors recommend against administration of rFVIIa for the reversal of VKA. (*Strong recommendation, low-quality evidence*)
6. If PCCs are not available or contraindicated, alternative treatment is recommended over no treatment. (*Strong recommendation, moderate-quality evidence*) Treatment choice may be guided by available therapies and patient-specific factors. (*Good Practice statement*)
    a. Treatment with FFP and vitamin K is recommended over no treatment. (*Strong recommendation, moderate-quality evidence*)
    b. The authors suggest dosing FFP at 10–15 ml/kg IV along with one dose of vitamin K 10 mg IV. (*Conditional recommendation, low-quality evidence*)

<u>Recommendations for Oral Direct Factor Xa Inhibitors Reversal</u>

1. The authors recommend discontinuing factor Xa inhibitors when intracranial hemorrhage is present or suspected. (*Good Practice statement*)
2. The authors recommend obtaining information on the time elapsed since the last dose of direct factor Xa inhibitor and possible medication interactions to assist in estimating the degree of anticoagulation exposure. (*Good Practice statement*)
3. The authors suggest that pharmacological reversal of oral factor Xa inhibitors should be guided primarily by bleeding (major or intracranial) and not primarily by laboratory testing. (*Conditional recommendation, low-quality evidence*)
4. The authors suggest administration of activated charcoal (50 g) to intubated intracranial hemorrhage patients with enteral access and/or those at low risk of aspiration who present within 2 h of ingestion of an oral direct factor Xa inhibitor. (*Conditional recommendation, very low-quality evidence*)
5. The authors suggest administering a 4-factor PCC (50 units/kg) or activated PCC (aPCC) (50 units/kg) if intracranial hemorrhage occurred within 3 to 5 terminal half-lives of drug exposure or in the context of liver failure. (*Conditional recommendation, low-quality evidence*)
6. The authors suggest administering 4-factor PCC or aPCC over rFVIIa because of the lower risk of adverse thrombotic events. (*Conditional recommendation, low-quality evidence*)

<u>Recommendations for Direct Thrombin Inhibitor (DTI) Reversal</u>

1. The authors recommend discontinuing direct thrombin inhibitors when intracranial hemorrhage is present or suspected. (*Good Practice statement*)
2. The authors recommend assessing the time and amount of the last ingested dose, renal function, and possible medication interactions to assist in estimating the degree of anticoagulation exposure. (*Good Practice statement*)
3. The authors suggest that pharmacological reversal of direct thrombin inhibitors should be guided primarily by bleeding (major or intracranial) and not primarily by laboratory testing. (*Conditional recommendation, low-quality evidence*)
4. The authors suggest administering activated charcoal (50 g) to intubated intracranial hemorrhage patients with enteral access and/or those at low risk of aspiration who present within 2 h of ingestion of an oral direct thrombin inhibitor. (*Conditional recommendation, very low-quality evidence*)
5. The authors recommend administering idarucizumab (5 g IV in two divided doses) to patients with intracranial hemorrhage associated with dabigatran if:
    a. The dabigatran was administered within a period of 3 to 5 half-lives and there is no evidence of renal failure (*Strong recommendation, moderate-quality of evidence*) or

   b. There is renal insufficiency leading to continued drug exposure beyond the normal 3 to 5 half-lives (*Strong recommendation, moderate-quality of evidence*)
6. The authors suggest administering aPCC (50 units/kg) or 4-factor PCC (50 units/kg) to patients with intracranial hemorrhage associated with direct thrombin inhibitors if idarucizumab is not available or if the hemorrhage is associated with a DTI other than dabigatran if:
   a. The direct thrombin inhibitor was administered within a period of 3 to 5 half-lives and there is no evidence of renal failure (*Conditional recommendation, low-quality evidence*) or
   b. There is renal insufficiency leading to continued drug exposure beyond the normal 3 to 5 half-lives. (*Conditional recommendation, low-quality evidence*)
7. In patients with dabigatran-associated intracranial hemorrhage and renal insufficiency or dabigatran overdose, the authors suggest hemodialysis if idarucizumab is not available. (*Conditional recommendation, low-quality evidence*)
8. In patients with dabigatran-associated intracranial hemorrhage who have already been treated with idarucizumab, PCC, or aPCC, with ongoing evidence of clinically significant bleeding, the authors suggest consideration of redosing idarucizumab and/or hemodialysis. (*Conditional recommendation, low-quality evidence*)
9. The authors recommend against administration of rFVIIa or FFP in direct thrombin inhibitor-related intracranial hemorrhage. (*Strong recommendation, low-quality evidence*)

Recommendations for Unfractionated Heparin (UHF) Reversal

1. The authors recommend discontinuing heparin infusions when intracranial hemorrhage is present or suspected. (*Good Practice statement*)
2. The authors recommend urgently reversing anticoagulation in patients who develop intracranial hemorrhage during full dose heparin infusion. (*Good Practice statement*)
3. The authors do not recommend routinely reversing prophylactic subcutaneous heparin. (*Good Practice statement*)
   a. The authors suggest considering reversal of prophylactic subcutaneous heparin if the activated partial thromboplastin time (aPTT) is significantly prolonged. (*Good Practice statement*)
4. The authors recommend administering intravenous protamine sulfate to reverse heparin in the context of intracranial hemorrhage. (*Strong recommendation, moderate-quality evidence*)
   a. The authors recommend dosing protamine according to the dose of heparin infused over the preceding 2 to 3 h. (*Strong recommendation, high-quality evidence*)
   b. The authors recommend dosing protamine sulfate at 1 mg for every 100 units of heparin given in the previous 2 to 3 h with a maximum single dose of 50 mg. (*Strong recommendation, moderate-quality evidence*)
   c. If the aPTT remains elevated, the authors suggest repeat administration of protamine at a dose of 0.5 mg protamine per 100 units of UFH. (*Conditional recommendation, low quality of evidence*)

Recommendations for Low-Molecular Weight Heparin (LMWH) Reversal

1. The authors recommend discontinuing LMWH when intracranial hemorrhage is present or suspected. (*Good Practice statement*)
2. The authors recommend reversing LMWH in patients with intracranial hemorrhage receiving therapeutic doses of LMWH. (*Strong recommendation, moderate-quality evidence*)
3. The authors recommend protamine administration by slow intravenous injection over a period of about 10 min according to the following dosing:
   a. For enoxaparin: If enoxaparin was given within 8 h, protamine sulfate should be administered at a dose of 1 mg per 1 mg of enoxaparin administered (up to a maximum single dose of 50 mg). If enoxaparin was given within 8 to 12 h, a dose of 0.5 mg of protamine per 1 mg of enoxaparin should be administered. After 3 to 5 half-lives have elapsed, protamine is probably not needed. (*Strong recommendation, moderate-quality evidence*)
   b. For dalteparin, nadroparin, and tinzaparin: Dose protamine at 1 mg per 100 anti-Xa units of LMWH administered in the past 3 to 5 half-lives of the drug, up to a maximum single dose of 50 mg. (*Strong recommendation, moderate-quality evidence*)
   c. If life-threatening bleeding persists, or the patient has renal insufficiency, the authors suggest redosing protamine (0.5 mg of protamine per 100 anti-Xa units or per 1 mg of enoxaparin). (*Conditional recommendation, very low-quality evidence*)
4. The authors suggest considering recombinant factor VIIa (90 mcg/kg IV) if protamine is contraindicated. (*Conditional recommendation, very low-quality evidence*)
5. The authors recommend against the reversal of LMWH in patients with intracranial hemorrhage receiving prophylactic dosing of LMWH. (*Good Practice statement*).
6. The authors suggest against reversing danaparoid with protamine. (*Conditional recommendation, low-quality evidence*)
7. The authors suggest reversing danaparoid with recombinant factor VIIa (90 mcg/kg IV once) in the context of intracranial hemorrhage. (*Conditional recommendation, very low-quality evidence*)

8. The authors suggest against using FFP, PCC, or aPCC to reverse LMWH. (*Conditional recommendation, low-quality evidence*)

Recommendations for Pentasaccharide Reversal

1. The authors recommend discontinuing pentasaccharides when intracranial hemorrhage is present or suspected. (*Good Practice statement*)
2. The authors suggest reversing pentasaccharides in patients with intracranial hemorrhage receiving full therapeutic doses. (*Good Practice statement*)
    a. The authors suggest administration of aPCC (20 units/kg) for reversal of pentasaccharides. (*Conditional recommendation, low-quality evidence*)
    b. If aPCC is contraindicated or not available, the authors suggest administration of rFVIIa (90 mcg/kg). (*Conditional recommendation, low-quality evidence*)
    c. The authors recommend against protamine for reversal of pentasaccharides. (*Strong recommendation, low-quality evidence*)
3. In intracranial hemorrhage patients receiving pentasaccharides for venous thromboembolism prophylaxis, the authors suggest against reversal unless there is evidence of bioaccumulation or impaired clearance. (*Good Practice statement*)

Recommendations for Thrombolytic Reversal

1. The authors recommend discontinuing thrombolytic agents when intracranial hemorrhage is present or suspected. (*Good Practice statement*)
2. The authors suggest using cryoprecipitate (10 units initial dose) in patients with thrombolytic agent-related symptomatic intracranial hemorrhage who have received a thrombolytic agent in the previous 24 h. (*Conditional recommendation, low-quality evidence*)
3. In cases where cryoprecipitate is contraindicated or not available in a timely manner, the authors suggest using an antifibrinolytic agent (tranexamic acid 10–15 mg/kg IV over 20 min or ε-aminocaproic acid 4–5 g IV) as an alternative to cryoprecipitate. (*Conditional recommendation, very low-quality evidence*)
4. The authors suggest checking fibrinogen levels after administration of reversal agents. If the fibrinogen is less than 150 mg/dL, the authors suggest administration of additional cryoprecipitate. (*Conditional recommendation, very low-quality evidence*)
5. It is unclear if platelet transfusion is useful and the authors cannot offer a recommendation at this time.

Recommendations for Antiplatelet Agent Reversal

1. The authors recommend discontinuing antiplatelet agents when intracranial hemorrhage is present or suspected. (*Good Practice statement*)
2. The authors suggest *against* platelet transfusion for patients with antiplatelet-associated intracranial hemorrhage who will *not* undergo a neurosurgical procedure, regardless of the type of platelet inhibitor, platelet function testing, hemorrhage volume, or neurological exam. (*Conditional recommendation, low-quality evidence*)
3. The authors suggest platelet transfusion for patients with aspirin- or adenosine diphosphate (ADP) inhibitor-associated intracranial hemorrhage who will undergo a neurosurgical procedure. (*Conditional recommendation, moderate-quality of evidence*)
    a. The authors recommend platelet function testing prior to platelet transfusion if possible. (*Strong recommendation, moderate-quality evidence*)
    b. When platelet function testing is not readily available, empiric platelet transfusion may be reasonable. (*Conditional recommendation, low-quality evidence*)
    c. The authors recommend against platelet transfusion for patients with laboratory documented platelet function within normal limits or documented antiplatelet resistance. (*Strong recommendation, moderate-quality evidence*)
4. The authors suggest against platelet transfusion in nonsteroidal anti-inflammatory drugs (NSAIDs) or glycoprotein IIb/IIIa inhibitor-related intracranial hemorrhage, even in the context of neurosurgical intervention. (*Conditional recommendation, very low-quality evidence*)
5. In candidates for platelet transfusion, the authors suggest an initial dose of one single-donor apheresis unit of platelets. Platelet testing is suggested prior to repeat platelet transfusion, if available and repeat transfusion should be used only for those with persistently abnormal platelet function tests and/or ongoing bleeding. (*Conditional recommendation, moderate-quality evidence*)
6. The authors suggest consideration of a single dose of desmopressin (DDAVP) in intracranial hemorrhage (0.4 mcg/kg IV) associated with aspirin/cyclooxygenase-1 (COX-1) inhibitors or ADP receptor inhibitors. In patients deemed appropriate (e.g., those undergoing a neurosurgical procedure), DDAVP can be used in addition to platelet transfusion. (*Conditional recommendation, low-quality evidence*)

Definitions

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Criteria for Quality of Evidence

Quality of Evidence	Description
High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Strength of Recommendation

Strength of Recommendation	Description
Strong	Most patients should receive the intervention.
Conditional	Most patients would benefit from the intervention, though some may not. The pros and cons of the intervention should be assessed taking into account the available evidence and the values and preferences of the patient.
Good Practice	There is a high confidence in the estimates of the effect of the intervention, but there is only indirect evidence that would be challenging to subject to a formalized Grading of Recommendations Assessment, Development and Evaluation (GRADE) evaluation.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Antithrombotic-associated intracranial hemorrhage

Guideline Category

Management

Treatment

Clinical Specialty

Critical Care

Emergency Medicine

Hematology

Neurology

Intended Users

Advanced Practice Nurses

Hospitals

Nurses

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

To provide timely, evidence-based reversal strategies to assist practitioners in the care of patients with antithrombotic-associated intracranial hemorrhage

Target Population

Adult patients with intracranial hemorrhage including subarachnoid hemorrhage (traumatic or spontaneous), intraparenchymal hemorrhage (traumatic or spontaneous), intraventricular hemorrhage, subdural hematoma, epidural hematoma, or traumatic brain injury

Interventions and Practices Considered

1. Vitamin K antagonists (VKAs)
    - Discontinuing VKAs
    - Vitamin K administration
    - 3-factor or 4-factor prothrombin complex concentrates (PCC)
    - Fresh frozen plasma (FFP)
2. Oral direct factor Xa inhibitors reversal
    - Discontinuing factor Xa inhibitors
    - Obtaining information on the time elapsed since the last dose of direct factor Xa inhibitor and possible medication interactions
    - Activated charcoal
    - 4-factor PCC or activated PCC (aPCC)
3. Direct thrombin inhibitor (DTI) reversal
    - Discontinuing direct thrombin inhibitors
    - Activated charcoal
    - Idarucizumab
    - aPCC or 4-factor PCC
    - Hemodialysis
4. Unfractionated heparin (UHF) reversal
    - Discontinuing heparin infusions
    - Intravenous protamine sulfate
5. Low-molecular weight heparin (LMWH) reversal
    - Discontinuing LMWH
    - Protamine administration
    - Recombinant factor VIIa (rFVIIa)
6. Pentasaccharide reversal
    - Discontinuing pentasaccharides
    - aPCC
    - rFVIIa
7. Thrombolytic reversal

- Discontinuing thrombolytic agents
- Cryoprecipitate
- Antifibrinolytic agent (tranexamic acid or ε-aminocaproic acid)
- Monitoring fibrinogen levels after administration of reversal agents

8. Antiplatelet agent reversal
    - Discontinuing antiplatelet agents
    - Platelet transfusion as indicated
    - Platelet function testing
    - Desmopressin (DDAVP)

Note: The authors considered but recommend against administration of rFVIIa or FFP in direct thrombin inhibitor-related intracranial hemorrhage; routine reversal of prophylactic subcutaneous heparin; reversal of LMWH in patients with intracranial hemorrhage receiving prophylactic dosing of LMWH; reversing danaparoid with protamine; using FFP, PCC, or aPCC to reverse LMWH; protamine for reversal of pentasaccharides; platelet transfusion for patients with antiplatelet-associated intracranial hemorrhage who will not undergo a neurosurgical procedure; platelet transfusion in nonsteroidal anti-inflammatory drug (NSAID) or glycoprotein IIb/IIIa-related intracranial hemorrhage.

Major Outcomes Considered

- Secondary hematoma expansion
- Increased risk of death
- Poor functional outcomes
- Morbidity
- Mortality

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The committee developed a comprehensive list of key search words including the generic and commercial names of the antithrombotic agents listed in the "Description of Methods Used to Formulate the Recommendations" field, intracranial hemorrhage, subarachnoid hemorrhage, intracerebral hemorrhage, intraparenchymal hemorrhage, subdural hematoma, subdural hemorrhage, intraventricular hemorrhage, epidural hemorrhage, epidural hematoma, and traumatic brain injury. A professional librarian organized this list of key words, developed medical subject heading (MeSH) terms, searched relevant clinical databases (including PubMed/Medline, Library of Science, the Cochrane database, EMBASE, and CINAHL), and created a database using Endnote^{TM} software. The original search included articles published through January 2013, and was limited to articles describing human subjects that were published in the English language. As guideline development progressed, committee members were responsible for updating the search intermittently to identify the more recent literature for inclusion (through November 2015). Clinical trials, meta-analyses, case series, preclinical studies and practice guidelines were all eligible for inclusion. Results were supplemented with the literature recommended by the committee or identified from reference lists.

The total number of articles identified via that primary search, inclusive of all drug classes, was 5,981. These articles were then subject to abstract review by the co-authors. During the abstract review, the following types of studies were excluded: animal studies, single case reports, review articles, editorial and opinion papers, articles not written in the English language, and articles not pertaining to the reversal of the antithrombotic class under review. This resulted in 368 articles, which were obtained in full text.

Number of Source Documents

Upon the authors' further review of the 368 full text articles, an additional 194 articles were identified that met the exclusion criteria listed above, leaving 174 articles included in the final systematic review and included in the evidentiary table of the guideline (see the "Availability of Companion Documents" field).

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence	Description
High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The literature findings were summarized in tables (see the "Availability of Companion Documents" field).

The writing committee reviewed articles selected from the database for inclusion in the treatment recommendations. The quality of evidence was analyzed, and treatment recommendations were drafted based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (see the "Rating Scheme for the Strength of the Evidence" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The Neurocritical Care Society along with the Society of Critical Care Medicine assembled a 13-person, international, multi-institutional committee with expertise in neurocritical care, neurology, neurosurgery, stroke, hematology, emergency medicine, pharmacy, nursing, hematopathology, and guideline development. The target population was adult patients with intracranial hemorrhage including subarachnoid hemorrhage (traumatic or spontaneous), intraparenchymal hemorrhage (traumatic or spontaneous), intraventricular hemorrhage, subdural hematoma, epidural hematoma, or traumatic contusion. Committee members were assigned one or more of the following sub-topic areas: vitamin K antagonists (VKAs), direct factor Xa antagonists, direct thrombin inhibitors, unfractionated heparin, low-molecular weight heparin, pentasaccharides, thrombolytics, and antiplatelet agents. The group did not address reversal of intrinsic coagulopathies such as those due to inherited hemophilia, liver, or renal disease.

The writing committee reviewed articles selected from the database for inclusion in the treatment recommendations. The quality of evidence was analyzed, and treatment recommendations were drafted, based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

The system allows for two grades of recommendations: "strong" and "conditional" (weak).

In certain circumstances, a strong recommendation can be made using low- or very low-quality evidence such as in the following five paradigms:

1. A life-threatening clinical situation in which the intervention may reduce mortality and the adverse effects are not prohibitive.
2. There is uncertain benefit to an intervention, but substantial established harm.
3. There is potential equivalence between treatment options, but one is clearly less costly or less risky.
4. There is high confidence in equivalence between treatment options, but one option is possibly more costly or risky.
5. The utility of the intervention is unknown, there is the possibility of harm and a high value is placed on avoiding potentially increased harm, which could be catastrophic.

The GRADE criteria also allow for the assignment of "Good Practice" statements. These statements imply high confidence in the estimates of the effect of the intervention, but are garnered from indirect evidence that would be challenging to subject to a formalized GRADE evaluation. Good practice statements should be actionable, necessary, have a large or unequivocal benefit, be based on data that are difficult to collect (or cannot be collected due to ethical or logistical reasons) and be based on a clear
rationale.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendation	Description
Strong	Most patients should receive the intervention.
Conditional	Most patients would benefit from the intervention, though some may not. The pros and cons of the intervention should be assessed taking into account the available evidence and the values and preferences of the patient.
Good Practice	There is a high confidence in the estimates of the effect of the intervention, but there is only indirect evidence that would be challenging to subject to a formalized Grading of Recommendations Assessment, Development and Evaluation (GRADE) evaluation.

Cost Analysis

The higher unit cost of prothrombin complex concentrates (PCC) compared to fresh frozen plasma (FFP) may lead some to believe that FFP may be more cost effective. However, the literature suggests the contrary. In a decision analysis comparing FFP to 4-factor PCC for the treatment of warfarin-associated life-threatening bleeding, the total cost of reversal was ≤15% of the hospitalization cost and PCC was found to be more cost-effective than FFP. The cost of intracranial hemorrhage expansion, longer length of stay, disability, lost productivity, and post-hemorrhage rehabilitation care that could occur with failure to rapidly correct the international normalizing ratio (INR), may outstrip the cost of the reversal agent. Furthermore, the increased cost associated with management of FFP-associated fluid overload has been found to defray the upfront cost of 4-factor PCC in the treatment of vitamin K antagonist (VKA)-associated bleeding.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

All committee members were in consensus with the recommendations presented in this guideline.

The Neurocritical Care Society and Society of Critical Care Medicine affirm the value of this guideline as an educational tool for clinicians.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Despite the delayed onset of action, vitamin K results in a sustained and durable reversal of anticoagulant activity and is therefore recommended in conjunction with other reversal agents. Small case-controlled studies suggest that protocol-driven administration of vitamin K along with fresh frozen plasma (FFP) or prothrombin complex concentrates (PCC) may improve functional outcomes and mortality rates.
- Several preclinical models have shown that 4-factor PCC (Beriplex/Kcentra) can reduce hematoma growth, and improve bleeding time, hemostasis, and mortality in dabigatran-exposed animals.
- One study found that protamine improves factor Xa activity in enoxaparin-exposed plasma, but only to approximately 40% of normal levels.

Potential Harms

- Caution should be exercised before using reversal agents in patients with concomitant life-threatening ischemia, thrombosis, or severe disseminated intravascular coagulopathy (DIC) because of the possibility of provoking thrombosis and ischemia.
- The risks of vitamin K are low. Anaphylactoid reactions are more common with intravenous administration; however, the incidence is only 3 per 10,000 doses. Reducing the infusion rate may reduce the risk, although this is controversial.
- Although fresh frozen plasma (FFP)-based strategies may be effective in reversing the international normalizing ratio (INR), the prolonged time to INR reversal limits the utility of FFP compared to other reversal strategies.
- As with all reversal agents, prothrombin complex concentrates (PCC) or activated PCC (aPCC) use is associated with a risk of complications. A wide range of thrombosis rates have been reported in patients receiving PCC products, although in controlled studies where patients with risk factors for thrombosis are excluded, the rates appear to be low (3.9%–7%). PCCs should be used with caution in patients who have evidence of acute arterial thrombus, DIC, or other coagulopathic states. Because of the rapid reversal action of PCC, a follow-up INR can be checked within 15 to 60 min of administration.
- Recombinant factor VIIa has been associated with a relatively high-thrombosis rate (12.8%–24%), likely due to the pro-coagulant state and thrombin burst associated with higher doses, though this is somewhat controversial. Patients with a concomitant hypercoagulable state or vascular injury are at higher risk of thrombotic complications, particularly arterial thrombosis.
- Administration of activated charcoal may be difficult and pose an aspiration risk in non-intubated patients with altered mental status. Therefore, it should be considered primarily in intubated patients with enteral access and in alert patients with minimal aspiration risk.
- Certain risks should be considered when using hemodialysis in patients with intracranial hemorrhage. First, there is the potential for exacerbation of cerebral edema by increasing brain water content through rapid urea reduction in the serum, which can lead to elevated intracranial pressure. Second, there is a risk of reduction of cerebral perfusion due to systemic hypotension. Even small fluctuations in blood pressure or electrolyte shifts may not be tolerated in an injured brain that does not auto-regulate appropriately. One way to counter these risks is to use continuous renal replacement therapy and reduce blood and dialysate flow rates. Unfortunately, high flow rates are needed to effectively eliminate dabigatran. In patients with intracranial hemorrhage associated with midline shift, mass effect, or edema, dialysis may not be well tolerated.
- In one study, adverse events associated with idarucizumab were mild (headaches and erythema at the infusion site) and similar in frequency to the placebo group. In another study, mild adverse events included infusion site erythema, hot flashes, epistaxis, hematuria, and infusion site hematoma.
- Adverse reactions to protamine (anaphylaxis, hypotension, bradycardia, and bronchoconstriction) are dose-dependent but can be attenuated by slowing the infusion. Patients who have previously received certain formulations of insulin (e.g., neutral protamine Hagedorn, or NPH), have undergone vasectomy, or have a known allergy to fish may be at increased risk of adverse reactions, as prior exposure can lead to antibodies against protamine sulfate. Patients considered at risk for allergy may be pre-treated with corticosteroids and histamines, although this has not been shown to definitively decrease the risk of adverse effects and should not delay reversal.
- Due to the high risk of both venous and arterial thrombosis, rFVIIa should be reserved for patients with a contraindication to protamine or

low molecular weight heparin (LMWH)-related bleeding refractory to protamine.
- Platelet transfusion is associated with serious risks including transfusion-related acute lung injury, thrombosis, disseminated intravascular coagulopathy, hemolytic transfusion reactions, and transfusion-associated sepsis, among others.
- Reported side effects of desmopressin (DDAVP) include facial flushing, peripheral edema, hypervolemia, decreased urine output, and hyponatremia. There are rare reports of cerebrovascular or cardiac thrombosis (<1%) with DDAVP use; therefore, caution should be applied in patients with recent ischemic stroke or acute myocardial infarction.

Contraindications

Contraindications

- The only available protease-activated receptor (PAR)-1 inhibitor (vorapaxar) is contraindicated in patients with a history of stroke, transient ischemic attack (TIA), or intracranial hemorrhage.
- Patients with cerebral venous thrombosis with concomitant intraparenchymal hemorrhage should not receive reversal agents due to the increased risk of hematoma expansion related to venous hypertension.

Qualifying Statements

Qualifying Statements

This guideline addresses commonly encountered antithrombotic-associated intracranial hemorrhage scenarios for which data and experience have been reported. Management of patients with complex situations (e.g., intracerebral hemorrhage with intrinsic coagulopathy, thrombocytopenia, disseminated intravascular coagulopathy [DIC], polytrauma, and/or concomitant ischemia or thrombophilia) will require prioritizing interventions and risk–benefit analyses. For these situations the information here should serve as a first guide, with reliance upon local and outside experts in a multidisciplinary team to help formulate treatment plans where necessary. This guideline did not specifically address antithrombotic reversal in a pediatric population.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

IOM Domain

Effectiveness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Frontera JA, Lewin JJ III, Rabinstein AA, Aisiku IP, Alexandrov AW, Cook AM, del Zoppo GJ, Kumar MA, Peerschke EI, Stiefel MF, Teitelbaum JS, Wartenberg KE, Zerfoss CL. Guideline for reversal of antithrombotics in intracranial hemorrhage: a statement for healthcare professionals from the Neurocritical Care Society and Society of Critical Care Medicine. Neurocrit Care. 2016 Feb;24(1):6-46. [434 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2016 Feb

Guideline Developer(s)

Neurocritical Care Society - Medical Specialty Society

Society of Critical Care Medicine - Professional Association

Source(s) of Funding

Neurocritical Care Society

Guideline Committee

Intracranial Hemorrhage Guideline Writing Committee

Composition of Group That Authored the Guideline

Committee Members: Jennifer A. Frontera (*Co-chair*), The Cerebrovascular Center, Neurological Institute, Cleveland Clinic and Case Western Reserve University, Cleveland, OH, USA; John J. Lewin III (*Co-chair*), The Departments of Pharmacy and Anesthesiology & Critical Care Medicine, The Johns Hopkins Hospital and Johns Hopkins University School of Medicine, Baltimore, MD, USA; Alejandro A. Rabinstein, The Department of Neurology, Mayo Clinic, Rochester, MN, USA; Imo P. Aisiku, Harvard Medical School, Brigham and Women's Hospital, Boston, MA, USA; Anne W. Alexandrov, The University of Tennessee Health Science Center, Memphis, TN, USA, Australian Catholic University, Sydney, Australia; Aaron M. Cook, Department of Pharmacy (UK Healthcare) & Department of Pharmacy Practice & Science (UK College of Pharmacy), University of Kentucky, Lexington, KY, USA; Gregory J. del Zoppo, The Departments of Medicine (Hematology) and Neurology, University of Washington School of Medicine, Seattle, WA, USA; Monisha A. Kumar, The Departments of Neurology, Neurosurgery, Anesthesiology & Critical Care, Perelman School of Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA, USA; Ellinor I. B. Peerschke, The Department of Laboratory Medicine and Pathology, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical School, New York, NY, USA; Michael F. Stiefel, The Department of Neurosurgery, Westchester Medical Center, New York Medical College, Valhalla, NY, USA; Jeanne S Teitelbaum, Hôpital du Sacré-Coeur and University of Montreal and Montreal Neurological Institute and McGill University, Montreal, Quebec, Canada; Katja E. Wartenberg, Klinik für Neurologie, Martin-Luther-Universität Halle-Wittenberg, Halle, Germany; Cindy L. Zerfoss, The Neuroscience and Neurosurgery Departments, Centra Lynchburg General Hospital, Lynchburg, VA, USA

Financial Disclosures/Conflicts of Interest

Dr. Aisiku serves on the National Advisory Board for the Medicines Company, Dr. Alexandrov serves on the speakers bureau for Genentech. Dr. del Zoppo has received research funds from the National Institutes of Health (NIH), Boehringer Ingelheim, and Novartis. He has served on advisory boards for Boehringer Ingelheim, Daiichi-Sankyo, and Novartis. Dr. Kumar has received support from Haemonetics. Dr. Stiefel serves as a consultant for Medtronic and Penumbra. The remaining authors have nothing to disclose.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Neurocritical Care Society Web site .

Availability of Companion Documents

Supplementary material is available from the Springer Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on July 19, 2016. The information was verified by the guideline developer on August 25, 2016.

Copyright Statement

Disclaimer

NGC Disclaimer

The National Guideline Clearinghouseâ„¢ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria.

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of

guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.